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Original Article

Efficacy and Safety of Nilotinib in Patients With *KIT*-Mutated Metastatic or Inoperable Melanoma: Final Results From the Global, Single-Arm, Phase II TEAM Trial

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Abstract

Background. The single-arm, phase II Tasigna Efficacy in Advanced Melanoma (TEAM) trial evaluated the KIT-selective tyrosine kinase inhibitor nilotinib in patients with *KIT*-mutated advanced melanoma without prior KIT inhibitor treatment.

Patients and Methods. Forty-two patients with *KIT*-mutated advanced melanoma were enrolled and treated with nilotinib 400 mg twice daily. TEAM originally included a comparator arm of dacarbazine (DTIC)-treated patients; the design was amended to a single-arm trial due to an observed low number of *KIT*-mutated melanomas. Thirteen patients were randomized to DTIC prior to the protocol amendment removing this study arm. The primary endpoint was objective response rate (ORR), determined according to Response Evaluation Criteria In Solid Tumors.

Results. ORR was 26.2% (*n*=11/42; 95% CI, 13.9%-42.0%), sufficient to reject the null hypothesis (ORR ≤10%). All observed responses were partial responses (PRs; median response duration, 7.1 months). Twenty patients (47.6%) had stable disease, 10 (23.8%) had progressive disease, and 1 (2.4%) response was unknown. Ten of the 11 responding patients had exon 11 mutations, 4 with an L576P mutation. The median progression-free survival and overall survival were 4.2 months and 18.0 months, respectively. Three of 13 patients on DTIC achieved a PR, and another patient had a PR following switch to nilotinib.

Conclusion. Nilotinib activity in patients with advanced *KIT*-mutated melanoma was similar to historical data from imatinib-treated patients. DTIC treatment showed potential activity, although the low patient number limits interpretation. Similar to previously reported results with imatinib, nilotinib showed greater activity among patients with an

exon 11 mutation, including L576P, suggesting that nilotinib may be an effective treatment option for patients with specific *KIT* mutations.

Clinical Trial Registration: ClinicalTrials.gov, NCT01028222

Keywords: KIT, melanoma, tyrosine kinase inhibitor, nilotinib, dacarbazine, imatinib

Key Message:

In a phase II, single-arm trial, the KIT-selective tyrosine kinase inhibitor nilotinib demonstrated activity in patients with *KIT*-mutated advanced melanoma. The activity of nilotinib was similar to historical data from imatinib-treated patients, suggesting that nilotinib may be an effective treatment option for patients with *KIT*-mutated melanoma.

Introduction

Mutations in the stem cell factor receptor tyrosine kinase gene (*KIT*) are observed in ≈2% of all melanomas [1], often leading to upregulated signaling from the corresponding protein KIT. *KIT* mutations are most common in acral and mucosal melanomas and less often observed in cutaneous melanoma arising from skin with chronic sun damage (CSD) [2]. *KIT* mutations are widely distributed over the coding region and observed in exons 9, 11, 13, 17, and 18 [2, 3]. Advanced melanomas with *KIT* aberrations (mutations and/or amplifications) have been shown to respond to the BCR-ABL1/KIT tyrosine kinase inhibitor (TKI) imatinib (Gleevec, Novartis Pharmaceuticals Corporation) [4-9], although response rates are low compared with BRAF inhibitors in *BRAF*-mutated melanomas [10, 11]. Nilotinib (Tasigna, Novartis Pharmaceuticals Corporation) has also demonstrated activity against several known *KIT* mutations in vitro, with potency comparable to or greater than that of imatinib (**Table S1**) [12, 13], and is less likely to lead to gastrointestinal or fluid retention–related adverse events (AEs) [14]. Nilotinib has thus been investigated as a potential treatment for *KIT*-mutated melanomas [15-18]. A phase II study in patients with advanced *KIT*-mutated melanoma reported partial responses (PRs) in 3 of 19 nilotinib-treated patients (15.8%), including 2 with prior imatinib resistance. The Tasigna Efficacy in Advanced Melanoma (TEAM; ClinicalTrials.gov, NCT01028222) trial was the first open-label, multicenter, single-arm, phase II study to assess the efficacy and safety of nilotinib in patients with *KIT*-mutated advanced melanoma without prior KIT inhibitor therapy.

Methods

Patients, Study Design, and Treatment

Patients were enrolled at 29 centers in 11 countries (Australia, Belgium, Brazil, Canada, China, Germany, Italy, Spain, Sweden, Switzerland, and the United States). Eligible patients were adults with histologically confirmed unresectable or metastatic acral, mucosal, or CSD melanoma without a history of brain metastases and with a confirmed *KIT* mutation in exons 9, 11, 13, or 17 (D820G, N822H, N822K, D820Y, Y822D, or Y823D), which have known KIT inhibitor sensitivity [4-6, 13]. Following a protocol amendment, patients with CSD melanoma were excluded from further enrollment because of a low observed *KIT* mutation rate. Mutation status was determined in a central laboratory (MolecularMD, Portland, OR) by DNA extraction from formalin-fixed, paraffin-embedded tumor tissue that was macrodissected, followed by polymerase chain reaction amplification and sequencing using a panel of direct sequencing assays with 20% mutant allele sensitivity. Germline DNA was not sequenced to determine if mutations were somatic.

Patients with *KIT* amplification without mutation were ineligible. Additional exclusion criteria included prior treatment with any TKI or >1 systemic anticancer therapy for melanoma in addition to any adjuvant therapy. Patients with significantly impaired cardiac function were ineligible, as were those with gastrointestinal impairment, chronic or acute pancreatitis, and/or acute or chronic liver or renal disease unrelated to melanoma.

Originally, the TEAM trial was a randomized, phase III study of nilotinib vs dacarbazine (DTIC; standard of care), with a target enrollment of 120 patients. This was amended to an open-label, single-arm design due to the rarity of patients harboring *KIT* mutations. Although 13 patients were randomized to DTIC prior to the protocol amendment and 10 eventually switched to nilotinib, the focus of this analysis is on the patients whose initial treatment was nilotinib. All patients assigned to nilotinib received nilotinib 400 mg twice daily. Dose adjustments were allowed per protocol-specified criteria (**Supplementary Methods**).

Study Endpoints and Assessments

The primary endpoint was the objective response rate (ORR), defined as the proportion of patients with a confirmed complete response (CR) or PR determined by the investigator according to Response Evaluation Criteria In Solid Tumors (RECIST). Tumor progression was assessed by computed tomography/magnetic resonance imaging or photography at screening, baseline, weeks 3, 6, 9, 12, 18, and 24, and every 12 weeks thereafter.

Key secondary endpoints included Kaplan-Meier (KM) estimates of progression-free survival (PFS; time from treatment start to date of first documented progression or death) and overall survival (OS; time from study start to date of death from any cause; **Supplementary Methods**). Additional secondary endpoints included KM-estimated duration of objective response (DOR; time from first documented CR or PR to first

documented progression or death) and disease control rate (DCR; proportion of patients with CR, PR, or stable disease [SD] for ≥12 weeks from start of treatment).

AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Safety was evaluated on an ongoing basis during study treatment and ≤30 days after the last dose of study treatment.

Statistical Analyses

Demographics, baseline characteristics, and efficacy analyses were determined in the intent-to-treat population, including all patients assigned to nilotinib. Patients randomized to DTIC prior to the study design amendment were analyzed separately. Demographics and baseline characteristics were summarized by descriptive statistics. Safety analyses were determined in the safety population, including all patients who received ≥1 dose of study medication.

For the primary endpoint, the null hypothesis (ORR ≤10%) was tested according to Simon's 2-stage design. After all 23 nilotinib-treated patients enrolled in the first stage had a confirmed response, discontinued the study, or completed 24 weeks of treatment, the trial was to be discontinued (null hypothesis accepted) if <3 confirmed responses were observed. If ≥3 confirmed responses were observed, the second stage would begin with an enrollment target of an additional 18 patients. If there were ≥9 responders overall, the null hypothesis would be rejected with a 1-sided significance level of 2.5% and a power of 90% against an alternative hypothesis of ORR ≥30%.

Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and local laws/regulations. Patients provided written informed consent prior to participation. The study protocol and all amendments were reviewed and approved by an institutional review board or independent ethics committee for each center.

Results

Patients and Treatment Exposure

Between 29 April 2010 and 23 October 2012, 877 patients were prescreened for *KIT* mutations. While a mutation frequency of 20%-30% was expected in the target population based on prestudy estimates [2], only 106 (12.1%) prescreened patients harbored *KIT* mutations (**Figure S1**). Of these, 78 were screened for eligibility per additional inclusion/exclusion criteria, and 55 enrolled. Primary reasons for screening failure were unacceptable laboratory or test procedure results (eg, brain metastasis). Prior to closure of the DTIC arm (via protocol amendment 27 July 2011), 14 and 13 patients were randomized to nilotinib and DTIC, respectively. Ten patients on DTIC subsequently crossed over to nilotinib; the remaining 3 discontinued (loss to follow-up, disease progression, administrative problems [*n*=1 each]). Herein, demographic, efficacy, and safety data are reported for patients who initiated nilotinib treatment upon enrollment (*N*=42), with brief mention of the DTIC results. Further details regarding efficacy/safety for patients randomized to DTIC are included in the **Appendix**.

In the nilotinib arm, acral and mucosal melanomas were most frequent (*n*=20; 47.6% each; information on primary site is in **Table 1)**; 2 patients (4.8%) had CSD melanoma of the head and neck (patients with CSD melanoma were excluded from the study following a protocol amendment). The most frequently observed *KIT* mutations were in exon 11 (*n*=26; 61.9%; most commonly L576P [*n*=10]) and exon 13 (*n*=13; 31.0%).

By study completion (last patient last visit, 31 December 2014), 38 patients (90.5%) had discontinued nilotinib, most commonly for disease progression (*n*=33; 86.8%). Known subsequent treatments following study discontinuation included chemotherapy/radiation (*n*=18), ipilimumab (*n*=15), imatinib (*n*=8), and other targeted/immune therapies (*n*=7). Four patients (9.5%) remained on nilotinib through a rollover study or local protocol. Median duration of nilotinib exposure was 15.0 weeks (range, 1-154 weeks). Dose interruptions due to AEs were reported in 26 patients (61.9%). Twenty-two patients (52.4%) received a reduced dose, with 6 patients having ≥1 direct dose reduction to 400 mg once daily without prior interruption. The lowest nilotinib dose received was 400 mg daily in 21 patients and 200 mg daily in 1 patient. The median percentage of days on study that patients received a full nilotinib dose was 75.5% (range, 12%-98%).

Efficacy

Among the 42 patients in the nilotinib arm, the ORR was 26.2% (95% CI, 13.9%-42.0%; PR, *n*=11; CR, *n*=0), sufficient to reject the null hypothesis of ORR ≤10% (**Table 2**). All responses occurred by 3 months; 5 occurred by 3 weeks and 7 by 6 weeks. Median DOR was 7.1 months (range, 2.8-34.6 months). Twenty patients (47.6%) had SD ≥6

weeks, 10 (23.8%) had progressive disease, and 1 (2.4%) response was unknown. The DCR was 47.6%. Three of 13 patients in the DTIC arm had a PR (ORR, 23.1%; CR, *n*=0; PR, *n*=3; **Tables S2 and S3**).

Response rate differed by mutation status; PR was observed in 10 of 26 patients (38.5%) with an exon 11 mutation, 1 of 13 patients (7.7%) with an exon 13 mutation, and 0 of 3 patients with an exon 9 or 17 mutation (**Figure 1A**). Of the 10 responding patients with an exon 11 mutation, 3 had the L576P mutation and 1 had a combined L576P/W557R mutation (**Table 3**). While the majority of observed mutations affect recurrently mutated sites and are thus considered likely to lead to constitutive KIT activation, a few of the identified mutations (ie, S476C and D496N in exon 9 and R634W in exon 13) affect nonrecurrent sites and therefore may not be pathogenic.

Thirty-five patients had PFS events (median PFS of 4.2 months; 95% CI, 2.1-5.8 months). At 6 months, the estimated PFS rate was 34.6% (95% CI, 20.2%-49.3%; **Figure 1B**). Among the 26 patients with an exon 11 mutation, median PFS was 5.4 months (95% CI, 2.7-8.3 months); the 6-month estimated PFS rate was 43.1% (95% CI, 23.4%-61.5%).

Twenty-six deaths occurred (due to melanoma [*n*=24], cardiopulmonary arrest [*n*=1], multiorgan dysfunction [*n*=1]). Of these, 1 death (due to melanoma) occurred within 30 days of discontinuation. No deaths were considered by the investigators to be attributable to nilotinib. Median OS was 18.0 months (95% CI, 10.9-20.3 months).

Estimated OS rates at 12 and 24 months were 63.6% (95% CI, 46.4%-76.6%) and 27.7% (95% CI, 13.3%-44.2%), respectively (**Figure 1C**). Among the 26 patients with an exon 11 mutation, 17 died on study and 3 were alive and receiving nilotinib with ≥25.8 months' follow-up. PFS and OS in DTIC-treated patients are shown in **Figure S2.**

Safety

Nilotinib was well tolerated, with a safety profile consistent with reports of nilotinib in patients with chronic myeloid leukemia [14]. No additional safety issues were observed on crossover to nilotinib, although data for this population are limited. Full safety data are provided in **Tables S4, S5, and S6**.

Discussion

Results from the TEAM trial showed that nilotinib is an active agent in patients with *KIT*-mutated metastatic melanoma. Similar results have been reported in other studies of nilotinib in patients with advanced melanoma with *KIT* aberrations, including patients with prior imatinib resistance [15-17]; response rates and survival in these nilotinib studies are similar to those in reports of imatinib treatment in patients with *KIT*-mutated melanoma (**Table S7**) [7-9].

Response rates to imatinib and nilotinib in patients with *KIT* mutations [7-9, 15-17] are approximately half of those observed in pivotal trials of BRAF inhibitors in patients with *BRAF*-mutated advanced melanoma [10, 11]. This may result from heterogeneity of *KIT* mutations relative to *BRAF* mutations (of which 74% are V600E) and/or a lower efficacy

of current KIT inhibitors [19]. Additionally, *RAS* mutations may confer resistance to KIT inhibitors [9]; although prior data suggest low incidences of concurrent *KIT*/*RAS* mutations [2, 9], the *RAS* mutation status of patients enrolled in TEAM is unknown.

Although the TEAM trial was not powered to statistically determine response rates according to mutation subtypes, numerical differences were observed by mutation. Patients with an exon 11 mutation had a better response rate than patients with an exon 13 mutation. Too few patients had exon 9 or 17 mutations to draw conclusions in these subpopulations. Consistent with prior studies of imatinib and nilotinib, the most frequently observed mutation among responding patients in TEAM was L576P on exon 11 [9, 16], a common KIT-activating mutation [2, 20]. Results from TEAM suggest that nilotinib may have activity in these patients, with 4 of 10 patients (40.0%) with L576P (including 1 with a concurrent W557R mutation) responding to nilotinib.

The response rate among DTIC-treated patients (23.1%) was higher than has been historically observed for DTIC [21], suggesting that patients enrolled in TEAM may have had less aggressive disease than the general population of patients with advanced *KIT*-mutated melanomas. Formal comparison of nilotinib and DTIC was not conducted due to partial randomization in the nilotinib arm and the very low number of patients in the DTIC arm. A randomized controlled trial of nilotinib vs standard of care in patients with advanced *KIT*-mutated melanoma may be needed to further evaluate nilotinib efficacy in this population. However, the inability to recruit a sufficient number of patients for a

randomized controlled trial demonstrates the difficulty of conducting large trials in uncommon molecular subsets of advanced diseases.

Potential limitations of this study include the lower enrollment target and changes in study design following the protocol amendments, which may have impacted the strength of the results. Additionally, the majority of patients had mucosal/acral melanoma, potentially limiting the generalizability of the findings to other subtypes known to harbor *KIT* aberrations, such as melanomas arising on skin with CSD. However, patients with mucosal/acral melanoma may be most appropriate for KIT inhibitor treatment because *KIT* mutations are most commonly observed in these subtypes [2].

Overall, nilotinib demonstrated activity in patients with advanced melanoma with *KIT* mutations without prior KIT inhibitor treatment. Although these data did not show an advantage for nilotinib relative to historical data with imatinib, they do suggest that nilotinib may be an additional treatment option for patients with *KIT*-mutated advanced melanoma, for example, in patients intolerant of imatinib. The treatment landscape for advanced melanoma is rapidly changing with the availability of immunotherapies such as inhibitors of programmed cell death protein 1 (eg, nivolumab, pembrolizumab) or cytotoxic T lymphocyte–associated protein 4 (eg, ipilimumab), which have shown activity in acral and/or mucosal melanomas (ORRs, 11.4%-23.3%) [22-24]. Thus, a potential role for KIT inhibitors may be in combination with or following disease progression on immunotherapy. Further studies are needed to investigate the potential efficacy of nilotinib in patients with advanced *KIT*-mutated melanoma, either in

combination with immunotherapy or in the setting of disease refractory to immunotherapy.

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Figure Legend

Figure 1. Tumor response and survival following nilotinib treatment. A) Best percentage change from baseline[a] and best overall response to nilotinib. B) Kaplan-Meier estimate of PFS[b]. C) Kaplan-Meier estimate of OS.

OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; UNK, unknown.

[a] Best percentage change from baseline determined from the sum of the longest diameter.

[b] Patients who discontinued due to disease progression without PD per RECIST were not considered to have had a PFS event.

Table 1. Demographics and baseline characteristics

Demographic variables	**Nilotinib 400 mg twice daily (*N*=42)**
Age, median (range), years	65.5 (20-87)
<65 years, n (%)	20 (47.6)
≥65 years, n (%)	22 (52.4)
Sex, n (%)	
Male	19 (45.2)
Female	23 (54.8)
Race, n (%)	
Caucasian	26 (61.9)
Asian	10 (23.8)
Other	6 (14.3)
WHO performance status, n (%)	
0	30 (71.4)
1	10 (23.8)
2	2 (4.8)
Melanoma type and primary site, n (%)	
Acral	20 (47.6)
Sole	8 (19.0)
Subungual (hand)	4 (9.5)
Subungual (foot)	2 (4.8)

Other[a]	6 (14.3)
Mucosal	20 (47.6)
Female genital tract	9 (21.4)
Anorectal	4 (9.5)
Head and neck	1 (2.4)
Other[b]	6 (14.3)
CSD	2 (4.8)
Head and neck	2 (4.8)
Lactate dehydrogenase, n (%)	
Within or below normal range	30 (71.4)
Above normal range	10 (23.8)
Missing	2 (4.8)
Prior systemic anticancer therapies,[c] n (%)	
Any therapy	13 (31.0)
Chemotherapy	9 (21.4)
Immunotherapy	2 (4.8)
Other[d]	6 (14.3)
KIT mutation status, n (%)	
Exon 11	26 (61.9)
L576P	10 (23.8)[e]
V559A	3 (7.1)
V560D	3 (7.1)
W557C	2 (4.8)

W557R	2 (4.8)
Other[f]	6 (14.3)
Exon 13	13 (31.0)
K642E	10 (23.8)
Other[g]	3 (7.1)
Exon 9[h]	2 (4.8)
Exon 17 (Y823D)	1 (2.4)
Time since initial diagnosis, median (range), months	13.2 (1.6-305.4)
Time since most recent recurrence/relapse, median (range), days	61 (1-761)

CSD, chronic sun damage; WHO, World Health Organization.

[a] Includes toe (*n*=4), heel (*n*=1), and thumb (*n*=1).

[b] Includes esophagus (*n*=3), nasal mucosa (*n*=2), and intranasal (*n*=1).

[c] Other than therapies received only in the adjuvant setting.

[d] Includes recombinant human endostatin injection (*n*=4), bleomycin (*n*=1), and sargramostim (*n*=1).

[e] Includes 1 patient with a combined L576P/W557R mutation.

[f] Other mutations detected were D572G, K558E, K581_P585dup, V559D, V569I, and W557hetdel (*n*=1 each).

[g] Other mutations detected were K642Q, R634W, and V654A (*n*=1 each).

[h] Specific mutations were D496N and S476C (*n*=1 each).

Table 2. Response to nilotinib, overall and by *KIT* mutation status

	Nilotinib 400 mg twice daily			
	Total (*N*=42)	**Exon 11 (*n*=26)**	**Exon 13 (*n*=13)**	**Other[a] (*n*=3)**
Best overall response, n (%)[b]				
CR	0	0	0	0
PR	11 (26.2)	10 (38.5)	1 (7.7)	0
SD	20 (47.6)	13 (50.0)	5 (38.5)	2 (66.7)
PD	10 (23.8)	3 (11.5)	6 (46.2)	1 (33.3)
Unknown	1 (2.4)[c]	0	1 (7.7)	0
ORR, % (95% CI)[d]	26.2 (13.9-42.0)	38.5 (12.1-39.5)	7.7 (0.1-12.6)	0 (0.0-8.4)
DOR, median (95% CI), months[e]	7.1 (4.2-not defined)	–	–	–
DCR, % (95% CI)[f]	47.6 (32.0-63.6)	61.5 (23.6-54.4)	30.8 (2.7-22.6)	0 (0.0-8.4)
PFS, median (95% CI), months	4.2 (2.1-5.8)	5.4 (2.7-8.3)	2.8 (1.3-8.6)	2.1 (1.9-2.8)
OS, median (95% CI), months	18.0 (10.9-20.3)	–	–	–

CR, complete response; DCR, disease control rate; DOR, duration of objective response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Exon 9 and exon 17 (Y823D).

[b] Percentages for each mutation subgroup are reported according to the number of patients in the respective mutational subgroups.

[c] This patient discontinued nilotinib on study day 11 and withdrew consent on study day 22.

[d] Rate of patients with CR + PR.

[e] Median DOR was determined among the 11 responding patients. Median DOR was not determined according to mutation subgroups; however, all responding patients had an exon 11 mutation except for 1 patient with a mutation on exon 13 (DOR, 4.2 months).

[f] Rate of patients with CR + PR + SD >12 weeks. SD in DCR is defined as lasting ≥12 week.

Table 3. Best overall response by *KIT* mutation

Patient	Melanoma type	Exon	*KIT* mutation	Baseline tumor size, cm	Best overall response	PFS, months	OS, months
1	Acral	11	L576P	7.6	PR	24.9[a]	25.8[b]
2	Mucosal	11	L576P	7.6	PR	5.4	9.4[c]
3	Mucosal	11	L576P	22.1	PR	4.1	21.0[b]
4	Acral	11	L576P	5.9	SD	2.1	6.6[c]
5	Mucosal	11	L576P	3.8	SD	2.8[a]	16.4[c]
6	Mucosal	11	L576P	12.3	SD	19.4	20.3[c]
7	Mucosal	11	L576P	3.3	SD	4.2	18.0[c]
8	Mucosal	11	L576P	28.1	SD	5.6	7.8[c]
9	Mucosal	11	L576P	2.2	PD	1.5	2.3[c]
10	CSD	11	V559A	2.0	PR	19.4	32.9[b]
11	Mucosal	11	V559A	2.1	SD	2.3[a]	18.5[d]
12	Acral	11	V559A	3.0	PD	0.7	1.0[b]

13	Acral	11	V560D	7.7	PR	8.6	23.5[c]
14	Acral	11	V560D	2.2	SD	8.2	14.7[c]
15	Acral	11	V560D	4.5	SD	2.7	6.0[c]
16	Acral	11	W557C	5.4	SD	2.1	18.5[c]
17	Acral	11	W557C	20.9	PD	0.7	1.4[c]
18	Acral	11	W557R	3.8	PR	35.4[a]	35.4[b]
19	Acral	11	W557R	5.6	SD	8.3	19.4[b]
20	Acral	11	D572G	1.0	SD	2.1	14.9[b]
21	Acral	11	K558E	9.2	SD	2.0	4.8[e]
22	Acral	11	K581_P585dup	3.0	PR	8.3	16.5[c]
23	Mucosal	11	L576P, W557R	9.2	PR	5.3	14.7[b]
24	Acral	11	V559D	6.9	PR	28.3[a]	28.3[b]
25	Mucosal	11	V569I	25.9	SD	5.3	5.3[c]
26	Mucosal	11	W557hetdel	10.5	PR	8.0	18.0[c]
27	Mucosal	13	K642E	1.2	PR	5.8	18.6[c]
28	Acral	13	K642E	5.2	SD	11.0	17.0[b]

29	Mucosal	13	K642E	25.6	SD	2.8	5.5[b]
30	Acral	13	K642E	10.1	SD	22.2[a]	22.9[b]
31	Acral	13	K642E	5.6	SD	8.6	11.6[c]
32	Mucosal	13	K642E	3.1	PD	1.5	17.8[b]
33	Mucosal	13	K642E	3.9	PD	0.7	15.9[c]
34	Acral	13	K642E	9.8	PD	1.4	6.4[c]
35	Mucosal	13	K642E	9.0	PD	1.3	10.9[c]
36	Mucosal	13	K642E	16.3	UNK	0.7[a]	0.7[b]
37	CSD	13	K642Q	4.4	PD	1.4	27.9[b]
38	Acral	13	R634W	12.4	PD	0.7	1.9[c]
39	Acral	13	V654A	5.2	SD	2.9	24.8[c]
40	Mucosal	9	D496N	1.8	PD	1.9	5.5[c]
41	Mucosal	9	S476C	17.9	SD	2.8	4.0[b]
42	Mucosal	17	Y823D	1.2	SD	2.1	9.7[c]

CSD, chronic sun damage; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UNK, unknown.

[a] Study day of censoring for PFS analysis. Patients were censored at the date of the last adequate tumor assessment (if they were alive and progression-free) or the first date of initiating other anticancer therapy.

[b] Study day of censoring for OS analysis. If death was not observed, patients were censored at day of last contact.

[c] Death due to study indication.

[d] Death due to multi-organ dysfunction.

[e] Death due to cardiopulmonary arrest.

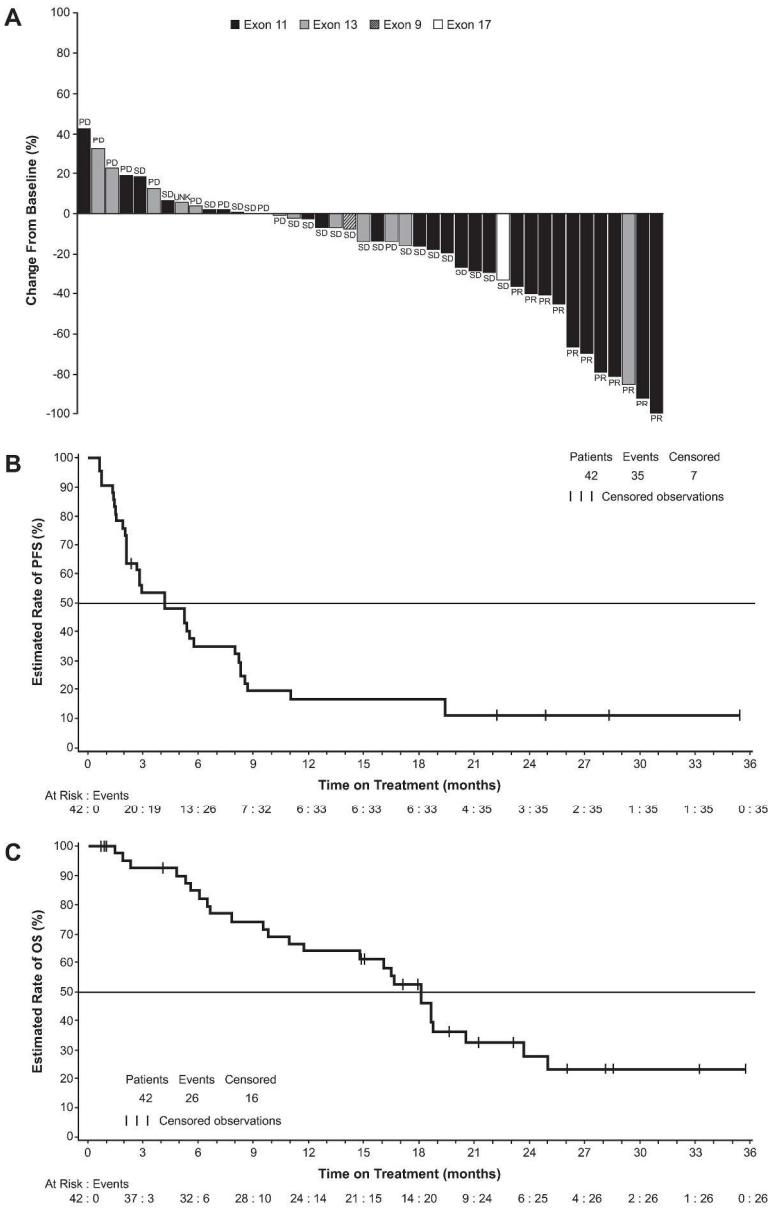

Figure 1. Tumor response and survival following nilotinib treatment. A) Best percentage change from baseline[a] and best overall response to nilotinib. B) Kaplan-Meier estimate of PFSb. C) Kaplan-Meier estimate of OS.

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Table 1. Demographics and baseline characteristics

Demographic variables	**Nilotinib 400 mg twice daily (*N*=42)**
Age, median (range), years	65.5 (20-87)
<65 years, n (%)	20 (47.6)
≥65 years, n (%)	22 (52.4)
Sex, n (%)	
Male	19 (45.2)
Female	23 (54.8)
Race, n (%)	
Caucasian	26 (61.9)
Asian	10 (23.8)
Other	6 (14.3)
WHO performance status, n (%)	
0	30 (71.4)
1	10 (23.8)
2	2 (4.8)
Melanoma type and primary site, n (%)	
Acral	20 (47.6)
Sole	8 (19.0)
Subungual (hand)	4 (9.5)
Subungual (foot)	2 (4.8)

Other[a]	6 (14.3)
Mucosal	20 (47.6)
Female genital tract	9 (21.4)
Anorectal	4 (9.5)
Head and neck	1 (2.4)
Other[b]	6 (14.3)
CSD	2 (4.8)
Head and neck	2 (4.8)
Lactate dehydrogenase, n (%)	
Within or below normal range	30 (71.4)
Above normal range	10 (23.8)
Missing	2 (4.8)
Prior systemic anticancer therapies,[c] n (%)	
Any therapy	13 (31.0)
Chemotherapy	~~8 (19.0)~~9 (21.4)
Immunotherapy	2 (4.8)
Other[d]	6 (14.3)
KIT mutation status, n (%)	
Exon 11	26 (61.9)
L576P	10 (23.8)[e]
V559A	3 (7.1)
V560D	3 (7.1)
W557C	2 (4.8)

W557R	2 (4.8)
Other[f]	6 (14.3)
Exon 13	13 (31.0)
K642E	10 (23.8)
Other[g]	3 (7.1)
Exon 9[h]	2 (4.8)
Exon 17 (Y823D)	1 (2.4)
Time since initial diagnosis, median (range), months	13.2 (1.6-305.4)
Time since most recent recurrence/relapse, median (range), days	61 (1-761)

CSD, chronic sun damage; WHO, World Health Organization.

[a] Includes toe (*n*=4), heel (*n*=1), and thumb (*n*=1).

[b] Includes esophagus (*n*=3), nasal mucosa (*n*=2), and intranasal (*n*=1).

[c] Other than therapies received only in the adjuvant setting.

[d] Includes recombinant human endostatin injection (*n*=4), bleomycin (*n*=1), and sargramostim (*n*=1).

[e] Includes 1 patient with a combined L576P/W557R mutation.

[f] Other mutations detected were D572G, K558E, K581_P585dup, V559D, V569I, and W557hetdel (*n*=1 each).

[g] Other mutations detected were K642Q, R634W, and V654A (*n*=1 each).

[h] Specific mutations were D496N and S476C (*n*=1 each).

Supplementary Appendix

Supplement to Guo J, Carvajal RD, Dummer R, et al. Efficacy and Safety of Nilotinib in Patients With *KIT*-Mutated Metastatic or Inoperable Melanoma: Final Results From the Global, Single-Arm, Phase II TEAM Trial

Supplementary Methods

Dose Adjustments

Dose adjustments (including interruption/reduction to nilotinib 400 mg once daily) were permitted for patients unable to tolerate the study dose per protocol-specified criteria. Dose interruption was recommended for patients with grade 3/4 hematologic or grade ≥ 2 nonhematologic adverse events. If these returned to grade 1, nilotinib could be reinitiated at 400 mg once daily. Re-escalation to 400 mg twice daily was allowed following resolution and/or management with supportive therapy for ≥ 1 month, except for patients with dose reductions due to QTc prolongation.

Study Endpoints and Assessments

Progression-free survival (PFS) was defined as the time from treatment start to the date of first documented progression or death. PFS time was censored for any patient alive and progression free at study end or when the patient received a new anticancer therapy. The date of censoring was the date of the last adequate tumor assessment prior to the end of study or the initiation of another anticancer therapy, whichever was earlier. Patients were not considered to have experienced a PFS event if they discontinued due to disease progression according to the investigator without documented progressive disease per Response Evaluation Criteria In Solid Tumors (RECIST) during tumor assessment. Overall survival was defined as the time from study start to the date of death from any cause. Surviving patients were censored at the latest date they were known to be alive.

Figure Legends

Figure S1. Screening, enrollment, and patient disposition

AE, adverse event; DTIC, dacarbazine.

[a] Patient discontinued treatment early due to non-compliance with study treatment.

[b] Patient discontinued treatment early because he/she was not followed with spiral computed tomography, as requested by the protocol.

[c] As of 31 Dec 2014, 4 patients enrolled in the nilotinib arm (median follow-up, 26.6 months) and 1 patient enrolled in the DTIC arm who crossed over to nilotinib treatment on study (duration of nilotinib treatment, 6.9 months) remained on nilotinib 400 mg twice daily after study completion through a rollover study or local protocol.

[d] Due to the amendment of the TEAM trial to a phase II, single-arm study of nilotinib efficacy and safety, no statistical comparisons were made between the nilotinib and DTIC study arms.

Figure S2. Kaplan-Meier estimates of (A) PFS[a] and (B) OS in the nilotinib and DTIC arms

DTIC, dacarbazine; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

[a] Patients who discontinued due to disease progression without progressive disease per RECIST were not considered to have had a PFS event.

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Table S1. Comparison of the effects of imatinib and nilotinib on wild-type and mutant KIT autophosphorylation and proliferation in cells

KIT mutant (cell type)	**Mean IC_{50} value, nM**			
	Imatinib		**Nilotinib**	
	Autophos-phorylation	Proliferation	Autophos-phorylation	Proliferation
Wild-type KIT (Ba/F3) [1]	ND	3132	ND	35
A502_Y503dup (Ba/F3)[a]	775	376	618	205
A502_Y503dup (Ba/F3) [2]	ND	509	ND	671
W557_K558del (Ba/F3) [2]	ND	460	ND	83
W557_K558delT670I (Ba/F3) [2]	ND	> 10,000	ND	> 10,000
V559D (Ba/F3) [1]	ND	63	ND	44
V559_V560del (Ba/F3)[a]	45	25	31	23
V559D/D820Y (Ba/F3) [2]	ND	3202	ND	297
V560delV654A (Ba/F3) [2]	ND	3927	ND	192
L576P (Ba/F3) [3]	ND	253	ND	185
R634W (Ba/F3)[a]	813	396	384	255
K642E (GIST882)[a]	96	120	210	158
T670I (Ba/F3) [2]	ND	> 10,000	ND	> 10,000
D816V (Ba/F3)[a]	> 10,000	> 10,000	5280	4570[b]
D816Y (Ba/F3)[a]	2400	3249	737	744
N822K (Ba/F3) [2]	ND	> 10,000	ND	3083
(Parental Ba/F3 + IL-3)[a]	NA	7384	NA	> 10,000

IC_{50}, half-maximal inhibitory concentration; NA, not applicable; ND, not determined

[a] Source: data on file.

[b] 4570 (*n* = 6) does not include 8 measures of > 10,000.

Table S2. Best overall response in DTIC-treated patients

Parameter	DTIC (*N* = 13)
Best overall response, n (%)[a]	
CR	0
PR	3 (23.1)
SD	6 (46.2)
PD	4 (30.8)
ORR (95% CI), %[b]	23.1 (5.0 to 53.8)
Median DOR (95% CI), months[c]	3.7 (2.8 to 12.7)
DCR (95% CI), %[d]	53.8 (25.1 to 80.8)
Median PFS (95% CI), months[e]	4.2 (0.8 to 8.0)
Median OS (95% CI), months[f]	22.8 (4.9 to not defined)

CR, complete response; DCR, disease control rate; DOR, duration of objective response; DTIC, dacarbazine; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Responses following crossover to nilotinib are not included. One additional patient achieved PR following switch to nilotinib.

[b] Rate of patients with CR + PR.

[c] Median DOR was determined among the 3 responding patients.

[d] Rate of patients with CR + PR + SD > 12 weeks. SD in DCR is defined as lasting $\geqslant$ 12 weeks.

[e] PFS was censored at the time of crossover to nilotinib treatment.

[f] OS analysis includes data obtained after crossover for the 10 patients who crossed over.

Table S3. Response by specific mutation in DTIC-treated patients

Patient	Melanoma type	Exon	*KIT* mutation	Baseline tumor size, cm	Best overall response	PFS, months	OS, months
1	Acral	11	L576P	11.6	PR	4.4	29.2[a]
2[b]	CSD	11	L576P	18.5	PR	14.1	23.9[c]
3[b]	Mucosal	11	L576P	22.6	PD	0.8	4.9[d]
4[b]	Mucosal	11	L576P	5.6	PD	1.2	7.8[d]
5[b]	Acral	11	V559A	2.2	PR	4.2	9.7[d]
6	Other	11	V559A	1	SD	2.7[e]	26.6[a]
7[b]	Acral	13	K642E	1.9	SD	1.6[e]	24.4[a]
8[b]	Mucosal	13	K642E	3.8	SD	5.5	13.1[d]
9[b]	Acral	13	K642E	1.3	SD	3.5	31.5[d]
10[b]	Mucosal	13	K642E	18	SD	8.0	21.7[d]
11	Acral	13	K642E	11.3	PD	0.7	0.9[a]
12[b]	Mucosal	17	Y823D	9.4	PD	0.7	3.1[d]
13[b]	Acral	9/11	A493V/ N567_T574 delinsKE	8.4	SD	2.1[e]	39.4[a]

CSD, chronic sun damage; DTIC, dacarbazine; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Study day of censoring for OS analysis. If death was not observed, patients were censored on day of last contact.

[b] Patient crossed over to nilotinib treatment on study.

[c] Death due to infection.

[d] Death due to study indication.

[e] Study day of censoring for PFS analysis. Patients were censored at the date of the last adequate tumor assessment (if they were alive and progression free) or the first date of initiating other anticancer therapy (including crossover to nilotinib treatment).

Table S4. Most frequently reported all-cause adverse events (⩾ 5%) in the nilotinib arm

	Nilotinib 400 mg twice daily (*N* = 42)	
Patients, n (%)	**All grades**	**Grade 3/4**
Total	41 (97.6)	25 (59.5)
Rash	20 (47.6)	1 (2.4)
Blood bilirubin increased	19 (45.2)	3 (7.1)
Nausea	18 (42.9)	2 (4.8)
Decreased appetite	13 (31.0)	0
Fatigue	13 (31.0)	0
Vomiting	12 (28.6)	2 (4.8)
Conjugated bilirubin increased	11 (26.2)	1 (2.4)
γ-Glutamyltransferase increased	11 (26.2)	5 (11.9)
ALT increased	10 (23.8)	2 (4.8)
Amylase increased	9 (21.4)	5 (11.9)
Unconjugated blood bilirubin increased	9 (21.4)	0
Constipation	9 (21.4)	0
Cough	9 (21.4)	0
Hyperglycemia	9 (21.4)	2 (4.8)
AST increased	8 (19.0)	0
Lipase increased	8 (19.0)	6 (14.3)
Diarrhea	7 (16.7)	1 (2.4)
Headache	6 (14.3)	0
Hypokalemia	6 (14.3)	4 (9.5)
Alopecia	5 (11.9)	0
Anemia	5 (11.9)	0
Blood alkaline phosphatase increased	5 (11.9)	0
Dyspnea	5 (11.9)	0
Hypocalcemia	5 (11.9)	0
Insomnia	5 (11.9)	0
Pain in extremity	5 (11.9)	0
Upper abdominal pain	4 (9.5)	1 (2.4)
Arthralgia	4 (9.5)	0
Blood lactate dehydrogenase increased	4 (9.5)	0
Blood pressure decreased	4 (9.5)	0
Dizziness	4 (9.5)	0
Hypercholesterolemia	4 (9.5)	0
Abdominal distension	3 (7.1)	0
Abdominal pain	3 (7.1)	1 (2.4)
Asthenia	3 (7.1)	1 (2.4)
Chills	3 (7.1)	0

Dyspepsia	3 (7.1)	0
Hyperkalemia	3 (7.1)	0
Hypertension	3 (7.1)	0
Hyperuricemia	3 (7.1)	0
Leukopenia	3 (7.1)	1 (2.4)
Lymphopenia	3 (7.1)	1 (2.4)
Nasopharyngitis	3 (7.1)	0
Peripheral edema	3 (7.1)	0
Pruritus	3 (7.1)	0
Pyrexia	3 (7.1)	1 (2.4)
Urinary tract infection	3 (7.1)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table S5. All-cause serious adverse events and adverse events of interest in the nilotinib arm

Patients, n (%)	Nilotinib 400 mg twice daily (*N* = 42)
Serious adverse events	12 (28.6)
Nausea	3 (7.1)
Vomiting	3 (7.1)
Abdominal pain	2 (4.8)
Lipase increased	2 (4.8)
Upper abdominal pain	1 (2.4)
Amylase increased	1 (2.4)
Angina pectoris[a]	1 (2.4)
Ankle fracture	1 (2.4)
Asthenia	1 (2.4)
Blood creatinine increased	1 (2.4)
Dehydration	1 (2.4)
Dizziness	1 (2.4)
Fatigue	1 (2.4)
Hematuria	1 (2.4)
Joint dislocation	1 (2.4)
Lower respiratory tract infections	1 (2.4)
Malaise	1 (2.4)
CNS metastasis	1 (2.4)
Pleural effusion	1 (2.4)
Visual impairment	1 (2.4)
Adverse events leading to discontinuation	2 (4.8)
Lipase increased	1 (2.4)
Nausea	1 (2.4)
Presyncope	1 (2.4)
Vomiting	1 (2.4)

CNS, central nervous system.

[a] This patient had a history of cardiac dysfunction; experienced grade 2 angina pectoris not suspected to be related to nilotinib on study day 3, followed by grade 3 angina pectoris not suspected to be related to nilotinib on study day 6 requiring hospitalization; was discontinued due to protocol deviation on study day 49; and died 3 months later due to cardiopulmonary arrest.

Table S6. Any-grade, all-cause adverse events in DTIC-treated patients

	DTIC (*N* = 13)	
Patients, n (%)	**All grades**	**Grade 3/4**
Total	9 (69.2)	2 (15.4)
Fatigue	5 (38.5)	–
Headache	5 (38.5)	–
Nausea	5 (38.5)	–
Pyrexia	3 (23.1)	–
Cough	2 (15.4)	–
Decreased appetite	2 (15.4)	–
Dizziness	2 (15.4)	–
Muscle spasm	2 (15.4)	–
Nasopharyngitis	2 (15.4)	–
Pain in extremity	2 (15.4)	–
Rash	2 (15.4)	–
Alopecia	1 (7.7)	–
ALT increased	1 (7.7)	–
Anxiety	1 (7.7)	–
AST increased	1 (7.7)	–
Asthenia	1 (7.7)	–
Blood bilirubin increased	1 (7.7)	–
Blood cholesterol increased	1 (7.7)	–
Blood pressure increased	1 (7.7)	–
Constipation	1 (7.7)	–
Depression	1 (7.7)	–
Diarrhea	1 (7.7)	–

Dry skin	1 (7.7)	–
Dyspepsia	1 (7.7)	–
Dyspnea	1 (7.7)	–
Ear infection	1 (7.7)	–
Peripheral edema	1 (7.7)	–
Erysipelas	1 (7.7)	–
Fall	1 (7.7)	–
Feeling cold	1 (7.7)	–
γ-Glutamyltransferase increased	1 (7.7)	–
Gastrointestinal infection	1 (7.7)	–
Gingivitis	1 (7.7)	–
Hemangioma	1 (7.7)	–
Hypercholesterolemia	1 (7.7)	–
Hyperglycemia	1 (7.7)	–
Hypertriglyceridemia	1 (7.7)	–
Insomnia	1 (7.7)	–
Lipase increased	1 (7.7)	–
Lymphedema	1 (7.7)	–
Monoplegia	1 (7.7)	–
Myalgia	1 (7.7)	–
Nasal congestion	1 (7.7)	–
Neutropenia	1 (7.7)	–
Neutrophil count decreased	1 (7.7)	1 (7.7)
Night sweats	1 (7.7)	–
Odynophagia	1 (7.7)	–
Oral discomfort	1 (7.7)	–
Oral herpes	1 (7.7)	–
Otorrhea	1 (7.7)	–
Paresthesia	1 (7.7)	–
Photosensitivity reaction	1 (7.7)	–

Platelet count decreased	1 (7.7)	1 (7.7)
Pneumonia	1 (7.7)	1 (7.7)
Pruritus	1 (7.7)	–
Skin burning sensation	1 (7.7)	–
Skin hypopigmentation	1 (7.7)	–
Throat irritation	1 (7.7)	–
Thrombocytopenia	1 (7.7)	–
Tumor pain	1 (7.7)	–
Vaginal hemorrhage	1 (7.7)	–
Vein disorder	1 (7.7)	–
Vomiting	1 (7.7)	–
Wheezing	1 (7.7)	–
Wound	1 (7.7)	–

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTIC, dacarbazine.

Table S7. Results from previous clinical trials of nilotinib or imatinib in patients with advanced *KIT*-mutated melanoma

	Population	Treatment	ORR, %	DOR, median (range), weeks	PFS/TTP, median (95% CI), months	OS, median (95% CI), months
Lee et al, 2015 [4]	Pts with *KIT* aberrations without prior KIT inhibitors (*N* = 42)	Nilotinib	16.7 Mutations: 22.2[a] Amplifications: 6.7	34 (5-55)	3.3 (1.6-4.9)	11.9 (7.1-16.7)
Lebbe et al, 2014 [5]	Pts with *KIT* aberrations without prior KIT inhibitors (*N* = 25)	Nilotinib	20[b]	ND	ND	ND
Carvajal et al, 2015 [6]	Pts with *KIT* mutations with prior KIT-inhibitor resistance (*N* = 20)	Nilotinib	18.2[c]	ND	3.4 (0.9-5.5)[c,d]	14.2 (7.1-NE)[c,d]
Carvajal et al, 2011 [7]	Pts with *KIT* aberrations (*N* = 28)	Imatinib	21.4[e]	ND (12-95)	2.8 (2.5-4.0)	10.7 (6.5-NE)
Guo et al, 2011 [8]	Pts with *KIT* aberrations (*N* = 43)	Imatinib	23.3[f]	ND	3.5	14.0
Hodi et al, 2013 [9]	Pts with *KIT* aberrations (*N* = 24 evaluable pts)	Imatinib	29.2[g]	ND	3.7 (2.6-5.6)	12.5 (8.8-18.0)

DOR, duration of response; ND, not determined; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pt, patient; TTP, time to progression.

[a] Of the 6 responding pts with *KIT* mutations, 5 had exon 11 mutations, including 3 with L576P.

[b] All responding pts had *KIT* mutations; exon 11 and 13 mutations were associated with response to nilotinib [10].

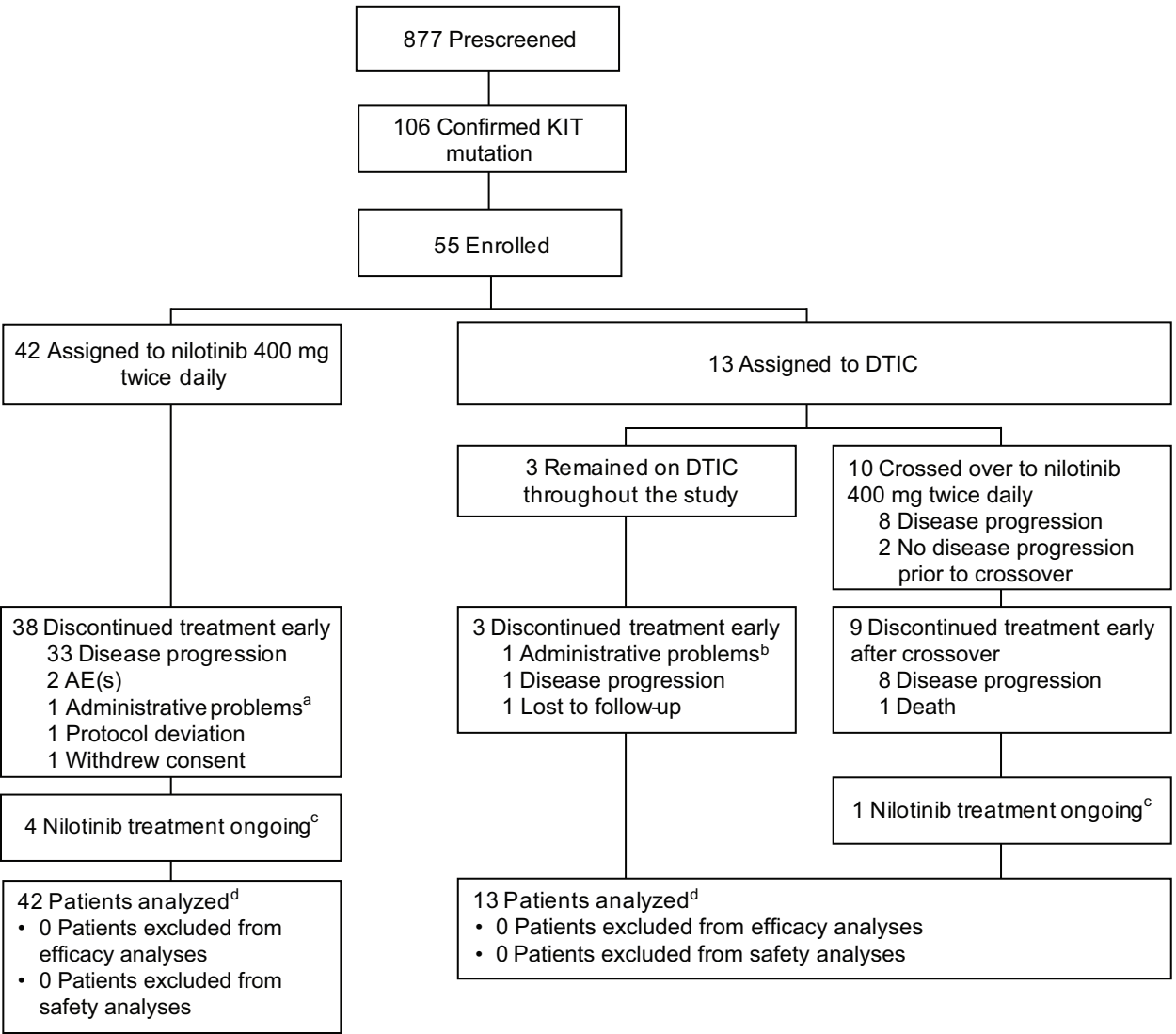
[c] Determined among the 11 pts without brain metastases.

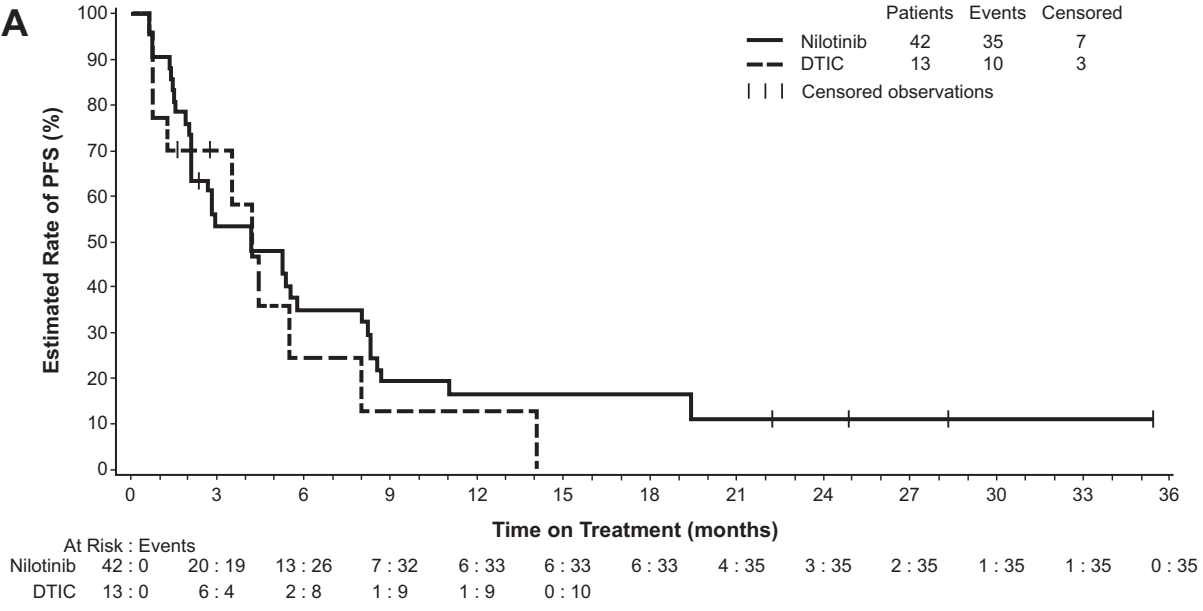
[d] In Carvajal et al, 2015, TTP and OS were reported with 90% CI.

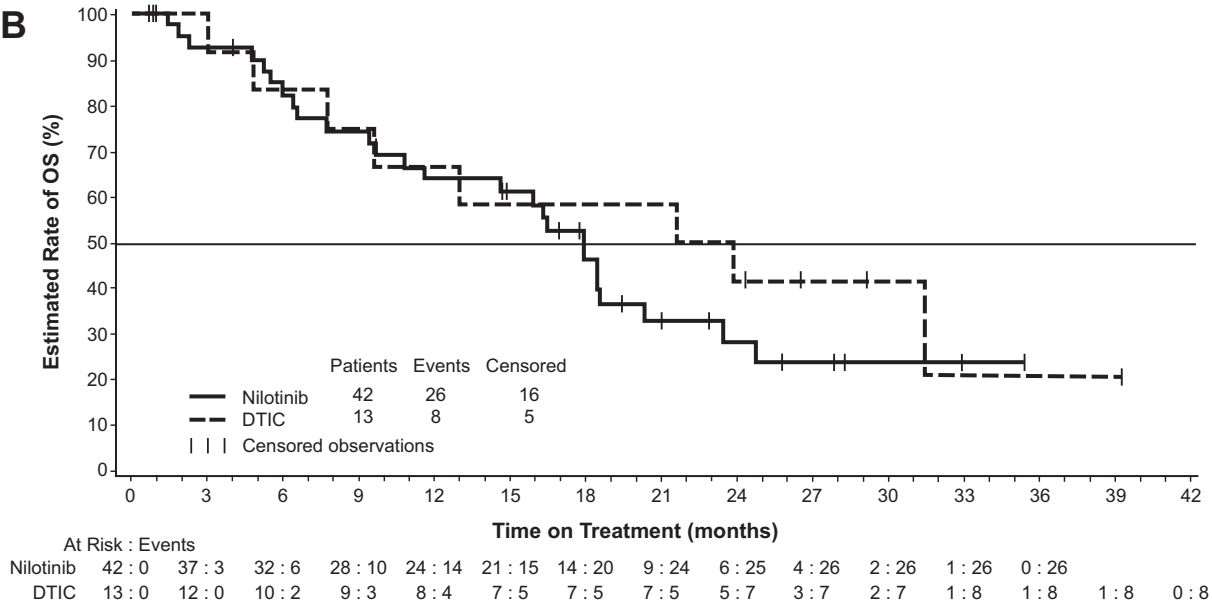
[e] All responding pts had L576P (exon 11) or K642E (exon 13) mutations.

[f] Nine of 10 responding patients had mutations in exon 11 or 13.

[g] All 7 responding patients had *KIT* mutations, of which 5 were in exon 11 (L576P; *n* = 3).


877 Prescreened
106 Confirmed KIT mutation
55 Enrolled
42 Assigned to nilotinib 400 mg twice daily
13 Assigned to DTIC
3 Remained on DTIC throughout the study
10 Crossed over to nilotinib 400 mg twice daily
8 Disease progression
2 No disease progression prior to crossover
38 Discontinued treatment early
33 Disease progression
2 AE(s)
1 Administrative problems[a]
1 Protocol deviation
1 Withdrew consent
3 Discontinued treatment early
1 Administrative problems[b]
1 Disease progression
1 Lost to follow-up
9 Discontinued treatment early after crossover
8 Disease progression
1 Death
4 Nilotinib treatment ongoing[c]
1 Nilotinib treatment ongoing[c]
42 Patients analyzed[d]
• 0 Patients excluded from efficacy analyses
• 0 Patients excluded from safety analyses
13 Patients analyzed[d]
• 0 Patients excluded from efficacy analyses
• 0 Patients excluded from safety analyses


A
Patients Events Censored
Nilotinib 42 35 7
DTIC 13 10 3
Censored observations
Estimated Rate of PFS (%)
Time on Treatment (months)
At Risk : Events
Nilotinib 42 : 0 20 : 19 13 : 26 7 : 32 6 : 33 6 : 33 6 : 33 4 : 35 3 : 35 2 : 35 1 : 35 1 : 35 0 : 35
DTIC 13 : 0 6 : 4 2 : 8 1 : 9 1 : 9 0 : 10


B
Patients Events Censored
Nilotinib 42 26 16
DTIC 13 8 5
Censored observations
Estimated Rate of OS (%)
Time on Treatment (months)
At Risk : Events
Nilotinib 42 : 0 37 : 3 32 : 6 28 : 10 24 : 14 21 : 15 14 : 20 9 : 24 6 : 25 4 : 26 2 : 26 1 : 26 0 : 26
DTIC 13 : 0 12 : 0 10 : 2 9 : 3 8 : 4 7 : 5 7 : 5 7 : 5 5 : 7 3 : 7 2 : 7 1 : 8 1 : 8 1 : 8 0 : 8